REMARKS

Status of the Claims

Claims 14-18 were previously presented and pending. Claim 14 is amended herein. Claims 15-18 are cancelled. Claims 19-25 are newly presented. Following entry of the amendment, claims 14 and 19-25 will be pending and at issue.

Support for the Amendments

Support for the amendment to the specification can be found in United States Provisional Patent Application No. 60/451,292, filed 2/27/2003 ("the '292 application") which was incorporated by reference. The text for new paragraph 59 is found in page 1 lines 4-7 of the '292 application. Therefore, the amendment to the specification introduce no new matter and its entry is respectfully requested.

Support for the amendment to the claim 14 can be found throughout the specification as filed, for example, in paragraphs [0017] and [0041]-[0046] of the Applicants' specification. Support for new claims 19-25 can be found throughout the specification, for example, in amended paragraph [0059] of the Applicants' specification. No new matter has been added and entry is respectfully requested.

Response to Objections to the Drawings

In the 2nd paragraph of the instant Office Action, the Examiner objects to replacement drawings. Figures 2, 3 and 6 as being illegible. Applicants respectfully traverse this rejection.

Figures 2, 3, and 6 are bar plot visualizations of protein structure alignments. In these visualizations, sub-portions of the proteins structures in the alignments are

shown in different colors corresponding to the "goodness" of the superposition between the two structures. The visualizations are only intended to show the relative proportions of the protein structures which have good alignments. The visualizations are not intended to show characters representing individual amino acids. Therefore, the visualizations as shown are legible as they adequately show the relative proportions of the protein structures which have good alignments.

Based on the above remarks, Applicants respectfully request that the Examiner reconsider and withdraw all objections to the drawings.

Response to Rejection under 35 U.S.C § 112, second paragraph

In the 3rd paragraph of the Office Action, the Examiner rejects claims 14-18 under 35 U.S.C § 112, second paragraph as allegedly failing to point out and distinctly claim the subject matter which the applicant regards as his invention. Specifically, the Examiner alleges that the specification fails to identifies variables k, X, S(F), S(LCS) and w used in the calculation of the scoring function. Applicants respectfully traverse this rejection.

The claimed method is directed to "generating a local-global alignment score based on the longest contiguous segment and the global distance test value." As claimed, the "longest contiguous segment" and the "global distance test value" can be combined in any way to generate the "local-global alignment score." The invention, as claimed does not imply the specific use of the formula referenced by the Examiner. Nor does the specification imply that the claimed invention is limited to the formula reference by the Examiner. For instance, paragraph [0036] recites "*A scoring function (LGA_S) can be defined as a combination of these values and can be used to evaluate the level of structure similarity of selected regions*." Paragraph

[0041] recites "The LGA scoring function has two components, LCS (Longest Continuous Segments) and GDT (Global Distance Test), established for the detection of regions of local and global structure similarities between proteins."

Paragraph [0046] of the Specification recites:

> "In the structure alignment search procedure, for each generated list of equivalent residues, the following values are calculated: LCS_vi - percent of residues (continuous set) that can fit under an RMSD cutoff of *vi* A (for *vi* = 1.0, 2.0, ...) and GDT_vi - an estimation of the percent of residues (largest set) that can fit under the distance cutoff of *vi* A (for *vi* = 0.5, 1.0, ...). A scoring function (LGA_S) can be defined as a combination of these values and can be used to evaluate the level of structure similarity of selected regions. For a given parameter w (0.0 <= w <= 1.0*)*, representing a weighting factor, we calculate LGA_S by the formula: LGA_S = *w* * S(GDT) + (I - *w)* * S(LCS) where S(F) function is defined as follows:
>
> foreach vi (v1, v2 • ... , vk) {
> Y= (k- i + 1)/k;
> X=X+ Y*F_vi;
> }
>
> S (F=X/ (1 + k) *k/2);"

Paragraph [0046] teaches that the variables **S(GDT)** and **S(LGA)** are calculated using the scoring function **S(F)**. Applicants respectfully request that the Examiner take official notice of the fact that the use of the variable '**F**' is standard mathematical notation used to represent a variable which is evaluated using a function. The amended paragraph further clarifies that the variable **w** is a "weighting factor" that takes a value between 0 and 1.

Paragraph [0046] further contains pseudocode which defines how the scoring function **S(F)** is used to generate the parameter **X** based on the values **vi** associated with the LCS and GDT. Applicants respectfully submit and request the Examiner to take official notice that those skilled in the art of bioinformatics readily understand that the referenced psuedocode represents a "loop". A loop is a programming

construct which iteratively performs a same sequence of instructions on a set of values. In program code, the value on the right hand side of an equation is evaluated first and assigned to the variable on the left hand side on an equation. At each iteration, the values **vi** are used to calculate intermediate values **Y** and **X**. The variable **k** is a subscript on **v** indicated the total number of values in the set of values **vi**. The value **Y** is calculated based on the variable **i** which represents the position of value the in the ordered set of values **vi** and the value **y** which represents the total number of values **vi** in the set of values. The value **X** is based on its previous value plus the new value of **Y** and **F_vi**, the score based on the value **vi** (e.g. **LCS_vi** or **GDT_vi**). Thus, the values **k** and **X** are well-defined to those skilled in the art of programming and bioinformatics.

Based on the above remarks, Applicants submit that the specification points out and distinctly claim the subject matter which the applicant regards as his invention. Reconsideration of the rejection and its withdrawal are respectfully requested.

The Examiner's rejections of claims 15 and 16 under 35 U.S.C § 112, second paragraph as allegedly failing allegedly failing to point out and distinctly claim the subject matter which the applicant regards as his invention (made in the 3rd paragraph of the Office Action) have been addressed by Applicants cancelling those claims without prejudice. Withdrawal of the rejection is respectfully requested.

Response to Rejections under 35 U.S.C § 112, first paragraph (new matter)

In the 4th paragraph of the Office Action, the Examiner rejects claims 14-18 under 35 U.S.C § 112, first paragraph for failing to comply with the written description requirement. In this rejection, the Examiner states that claim 14

introduces a new term "global distance metric" which is not defined in the specification. Applicants respectfully traverse this rejection.

As amended, claim 1 recites "global distance test value", which is supported in the instant specification, for example, at paragraph [0041], "*The LGA scoring function has two components, LCS (Longest Continuous Segments) and GDT (Global Distance Test), established for the detection of regions of local and global structure similarities between proteins.*" Applicants submit that claim 14, as amended, reasonably conveys to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention. Therefore, Applicant respectfully request that the Examiner reconsider and withdraw this rejection.

Response to Rejections under 35 U.S.C § 101 (utility)

In the 6th paragraph of the Office Action, the Examiner rejects claims 14-18 as allegedly being directed to non-statutory subject matter. Specifically, the Examiner alleges that the instant claims do not produce a tangible result. In support of this allegation, the Examiner states that "method as claimed may take [place] entirely within the confines of a computer without any communication to the outside world".

Claim 14, has been amended to clarify that the method is a "computer-implemented method". Support for this amendment can be found, for example at , paragraph [0059] of the instant specification which has been amended to recite portions of the '292 application which discuss the use of LGA as an online service.

Claim 14, has been further amended to recite "providing a result based on the

local-global alignment score". Support for this amendment can be found throughout the specification as filed. The specification teaches many different methods of "providing a result based no the local global alignment score" such as outputting a text-only output (*see* Specification, paragraph [0048]), a bar plot (*see* Specification paragraphs [0050]-[0051] and Figs. 2 and 3) and a plot of a three dimensional protein structure (*see* Specification paragraphs [0051] and [0056]).

Based on the above remarks, Applicants submit that claim 14 is directed to statutory subject matter. Therefore, Applicant respectfully request that the Examiner reconsider and withdraw this rejection.

Response to Rejection Under 35 U.S.C § 102(b)

In the 7th paragraph of the Office Action, the Examiner rejects claim 14 as allegedly being anticipated by Zemla et al. (Proteins: Structure, Function, and Genetics vol. 45, Issue S) or Cristobal et al. (BMC Bioinformatics 2001, 2:5, Published August 1st 2001).

Claim 14 has been amended to recite elements similar to those of cancelled claims 15-18. In the Office Action, cancelled claims 15-18 were rejected under 35 USC § 103(a). Therefore, the rejection under 35 USC § 102 is moot as drawn to amended claim 14. Amended claim 14 is discussed below with respect to the rejection under 35 USC § 103(a).

Response to Rejection Under 35 U.S.C § 103(a)

In the 8th paragraph of the Office Action, the Examiner rejects claims 14-18 under 35 U.S.C § 103(a) as allegedly unpatentable over Zemla or Cristobal in further view of Cristobal. Applicants respectfully traverse this rejection.

Claim 14 has been amended to recite elements similar to those of cancelled claims 15-18. Specifically, claim 14, as amended, recites:

> A computer-implemented method of generating a local-global alignment score which indicates a global and a local similarity between a first protein structure and a second protein structure, the method comprising:
> receiving a protein structure correspondence wherein a plurality of positions in the protein structure correspondence indicates a corresponding pair of residues in the first protein structure and the second protein structure;
> determining a plurality of root mean square deviations corresponding to a plurality of sets of pairs of residues, wherein each set of pairs of residues comprises a plurality of pairs of residues that are contiguous in the protein structure correspondences and the plurality of root mean square deviations are determined using a plurality of specified threshold values;
> selecting a longest contiguous segment corresponding to a set of pairs of residues of the plurality of pairs of residues based on the plurality of root mean square deviations;
> identifying a plurality of distance scores, wherein each distance score corresponds to a number of pairs of residues in the correspondence that are within a pre-defined distance of a plurality of pre-defined distances
> selecting a global distance test value based on the plurality of distance scores;
> generating the local-global alignment score based on the longest contiguous segment and the global distance test value; and
> providing a result based on the local-global alignment score.

Claims 19-25 depend from claim 14 and include these elements.

In the clamed invention, a protein structure correspondence is received wherein a plurality of positions in the protein structure correspondence indicates a corresponding pair of residues in the first protein structure and the second protein structure (e.g., *see* Specification [0041], "*the LGA program generates many different local superpositions to detect regions where proteins are similar*"). A plurality of root mean square deviations corresponding to a plurality of sets of pairs of residues is determined (e.g., see Specification [0042], "*LCS results are generated for a set of increasing RMSD cutoffs (1Å (Angstrom), 2 Å, and 5Å), and in the GDT analysis,*

two structures are scanned every 0.5 Å, starting from 0.5 Å up to a 10.0 Å distance cutoff"). A longest contiguous segment corresponding to a set of pairs of residues of the plurality of pairs of residues based on the plurality of root mean square deviations (e.g., *see* Specification [0041] "*the LCS procedure is able to localize and superimpose the longest segments of residues that can fit under a selected RMSD cutoff*"). A plurality of distance scores is identified, wherein each distance score corresponds to a number of pairs of residues in the correspondence that are within a pre-defined distance of a plurality of pre-defined distances (e.g. *see* Specification [] ""). A global distance test value is selected based on the plurality of distance scores (e.g., *see* Specification [0042], "*Each calculated superposition is used as a staring point to give an initial list of equivalent residues. The list of equivalent residues is iteratively extended to collect the largest set of residues that can fit under a given distance cutoff.*"). A local-global alignment score based on the longest contiguous segment and the global distance test value is generated and stored (e.g., *see* Specification [0046], "*LCS_vi – percent of residues (continuous set) that can fit under an RMSD cutoff of vi A (for vi = 1.0, 2.0 ...), and GDT_vi- an estimation of the percent of residues (largest set) that can fit under the distance cutoff of vi A (for vi -= 0.5, 1.0, ...). A scoring function (LGA_) can be defined as a combination of these values and can be used to evaluate the level of structure similarity of selected regions*)".

Claim 14, recites elements of cancelled claims 15-18. In the Office Action, the Examiner alleges that the methods outlined in 15-18 are obvious in view of Zemla in view of Cristobal. Specifically, the Examiner states that Cristobal teaches that "for automatic assessment of protein structure, the best approach is to combine

sequence-independent and sequence-dependent methods". The Examiner further states that "*Applying the KSR standard of obviousness to the reference of Cristobal, examiner concluded that the combination of sequence-independent and sequence-dependent methods is an "obvious to try" choosing from a finite number of predictable solution*s".

Applicants respectfully traverse the rejection by amendment and argument. Claim 14, as amended, recites a method in which a longest continuous segment is selected based on a plurality of root mean square deviations which are "determined using a plurality of specified threshold values." *See* Zemla Declaration at ¶5. Similarly, a global distance test value is selected based on a plurality of distance scores which represent a number of residue pairs within "a pre-defined distance of a plurality of pre-defined distances." *See* Zemla Declaration at ¶6. This selection of both the longest continuous segment and the global distance test value is based on a plurality of parameters such as "a plurality of specified threshold values" and "a plurality of pre-defined distances" is beneficial as this allows for the evaluation of many intermediate protein structure superpositions. *See* Zemla Declaration at ¶10 and ¶11. The benefit of selecting both the longest continuous segment and the global distance test value based on a plurality of parameters is evidenced by the unexpected results obtained from combining these methods. *See* Zemla Declaration at ¶¶13-15.

Cristobal does not teach or suggest these elements of the claimed invention. At best, Cristobal teaches metrics for evaluating protein structure alignments. *See* Zemla Declaration at ¶18. The metrics taught by Cristobal do not imply selecting a value such as a "global distance test value" or a "longest continuous segment" based

on a plurality of values generated using a plurality of different parameters such as "a plurality of pre-defined distances" or "a plurality of specified threshold values". *See* Zemla Declaration at ¶¶17 and 18. Further, the method of calculating the global distance value based on an **average** of a plurality of distance scores taught by Cristobal and referenced by the Examiner, teaches away from the claimed method of "selecting a global distance test value based on the plurality of distance scores". *See* Zemla Declaration at ¶17. Therefore, Cristobal fails to teach or suggest these elements of the claimed method. *See* Zemla Declaration at ¶19. As such, it cannot render obvious the instantly-claimed invention.

Based on at least the above, Applicants submit that claim 14 is patentably distinguishable over Zemla and Cristobal, alone or in the combination suggested by the examiner. Claims 19-25 depend from Claim 14 and are patentably

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distinguishable over Zemla and Cristobel for at least the same reasons. Thus, Applicants respectfully request that the Examiner reconsider this rejection and withdraw it.

CONCLUSION

Withdrawal of the pending rejections and reconsideration of the claims are respectfully requested, and a notice of allowance is earnestly solicited. If the Examiner has any questions concerning this Response, the Examiner is invited to telephone Applicants' representative at (415) 875-2413.

Respectfully submitted,
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